Epilepsi 2021;27(2):113-118 DOI: 10.14744/epilepsi.2020.98705

ORIGINAL ARTICLE

Febrile Seizures in Idiopathic/Genetic Generalized and Self-Limited Focal Epilepsies

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Abstract

Objectives: Febrile seizure (FS) is the most common form of childhood seizures. Furthermore, idiopathic/generalized and focal/self-limited epilepsies present at the similar age-range. They usually have a favorable outcome. This study was conducted to investigate the prevalence and demographic profile of FS in patients with idiopathic/generalized and focal/self-limited epilepsies.

Methods: This retrospective study included all of the patients with normal developmental assessments who were admitted to our outpatient clinic with idiopathic/generalized and focal/self-limited epilepsy. The data were collected from their medical and electroencephalogram records. The patients were subgrouped according to their syndromes and the presence of FS. Comparisons were made for the characteristics of FS.

Results: Among 320 patients with the diagnosis of focal or generalized epilepsy with presumed genetic cause, FSs were present in 14.7% (n=47) of them without gender preponderance. Self-limited focal epilepsy was present in 232 children (72.5%). The mean age of epilepsy onset was 7.97±3.38 years (range: 1–18 years). Although the distribution of FSs in focal or generalized epilepsy groups (p=0.552) and subtypes of these groups (p=0.701) did not indicate any statistical significance, highest ratios of FS occurrence were found in juvenile myoclonic epilepsy and idiopathic photosensitive occipital lobe epilepsy groups.

Conclusion: Gender, family history of epilepsy and FS, onset age of epilepsy, type of epilepsy did not seem as a predictor factor for subsequent epilepsy in the patients with FS otherwise normal children.

Keywords: Febrile seizure; focal/self-limited epilepsy; idiopathic/generalized epilepsy.

Cite this article as: Tümay F, Nalbantoglu M, İnan R, Yavlal F, Demirbilek V. Febrile Seizures in Idiopathic/Genetic Generalized and Self-Limited Focal Epilepsies. Epilepsi 2021;27:113-118.

Introduction

Febrile seizure (FS) is defined by the International League against Epilepsy (ILAE) as a type of seizure associated with the fever arising from an infection outside the central nervous system in the absence of acute electrolyte imbalance or prior afebrile seizures (AFSs). The lower age limit refers to being older than 1 month of age.[1] Although the definition lacks an upper age limit, presentation after 7 years of age is quite rare. Mostly, FS occurs between 6 months and 5 years of age with the peak incidence at 18 months.[2,3]

FS is the most common form of childhood seizure.[4] Its prevalence ranges from 2% to 4% in the western countries with an ethnic variability (9–10% for Japanese, and up to 14% in Guam).[3] It reoccurs in one-third of the children and its association with epilepsy is low (2.4% of the neurologically normal children with FS compared to 1.4% of general population).[5] Genetic (especially genes coding ion channels) and environmental factors are considered to be responsible for FS.[6,7]

In terms of epilepsy, traditionally, the idiopathic/presumed genetic cause was used to implicate the age-related onset,


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Received 25.04.2020
Accepted 09.11.2020
Online date 02.04.2021

İdiyopatik/Genetik Jeneralize ve Kendini Sınırlayan Fokal Epilepsilerde Febril Nöbetler

Öz

Amaç: Febril nöbet (FN) çocukluk çağı döneminin en sık görülen nöbet tipidir. İdiyopatik/jeneralize ve fokal/ kendini sınırlayan nöbetler de aynı yaş grubunda izlenmektedir. Genellikle iyi seyirlidirler. Bu çalışma idiyopatik/jeneralize ve fokal/ kendini sınırlayan epilepsileri olan hastalarda FN prevalansı ve demografik profili araştırmak amacıyla yapılmıştır.

Gereç ve Yöntem: Bu geriye dönük çalışmaya polikliniğimize başvurmuş, gelişimsel değerlendirmeleri normal olan idiyopatik/jeneralize ve fokal/ kendini sınırlayan epilepsileri olan hastalar dahil edildi. Veriler hastaların tıbbi ve EEG kayıtlarından toplandı. Hastalar sendromlarına ve FN varlığına göre alt gruplara ayrıldı. Karşılaştırmalar FN özelliklerine göre yapıldı.

Bulgular: Fokal ya da olası genetik nedenli jeneralize epilepsi tanılı 320 hasta arasında, FN'ler cinsiyet üstünlüğü olmaksızın %14.7 (n=47) hastada mevcuttu. Kendini sınırlayan fokal epilepsi 232 çocukta (%72.5) mevcuttu. Epilepsi başlangıç ortalama yaşı 7.97±3.38 yıldı (1–18 yıl). FN'lerin fokal ya da jeneralize epilepsi grupları (p=0.552) ya da bu grupların alt tipleri (p=0.701) içindeki dağılımı istatiksel anlamlılık göstermemekle birlikte, FN varlığı en yüksek oranla jüvenil miyoklonik epilepsi ve idiyopatik fotosensitif oksipital lob epilepsi gruplarında bulundu.

Sonuç: Cinsiyet, FN ya da epilepsi aile öyküsü, epilepsi başlangıç yaşı, epilepsi tipi FN dışında normal olan çocuklarda ortaya çıkacak epilepsi için belirleyici bir faktör olarak görünmemektedir.

Anahtar sözcükler: Febril nöbet; fokal/ kendini sınırlayan epilepsi; idiyopatik/jeneralize epilepsi.

highly pharmacoresponsive characteristics and a presumed genetic background for children.[8] Considering these features, presumed genetic background and favorable outcome seems to be common for childhood epilepsies and FS. The present study aimed to investigate the frequency of FS in focal/self-limited and idiopathic/generalized childhood epilepsies to explore the relationship between FS and epilepsy.

Materials and Methods

This was a retrospective cross-sectional study conducted at Cerrahpaşa School of Medicine, Pediatric Neurology Clinics of Neurology Department. The medical records of all patients followed in our outpatient clinic with diagnosis of idiopathic/genetic epilepsy beginning at pediatric age were investigated retrospectively. Their medical histories and family histories including epilepsy and FS were examined. The inclusion criteria were composed of having idiopathic/genetic childhood epilepsy along with normal birth history, normal neurological examination, and normal developmental assessments including cognitive, speech, and motor skills. For each patient, parameters such as gender, onset age of epilepsy, seizure type (focal/generalized), and history of FSs were collected from their medical records.

The diagnosis of epilepsy was made on the basis of clinical and electroencephalogram (EEG) findings as recommended by the Commission on Classification and Terminology of the ILAE, 2017.[9–11] Patients were initially classified into two groups according to the mode of seizure onset, namely, focal and generalized seizures. Epilepsy syndrome diagnosis was made on the basis of age of seizure onset, seizure types, and EEG characteristics. Patients having focal epilepsy were subgrouped as childhood epilepsy with centrotemporal spikes, Panayiotopoulos syndrome, childhood occipital epilepsy (Gastaut type), and idiopathic photosensitive occipital lobe epilepsy (IPOE). Patients with generalized epilepsy were subgrouped as childhood absence epilepsy (CAE) and juvenile myoclonic epilepsy (JME). The inclusion criteria for FSs were having seizures triggered exclusively by high fever without evidence of infection of the central nervous system.[1]

The Statistical Package for the Social Sciences (SPSS, Chicago, IL, U.S.A.). was used for statistical analysis. The differences among demographic variables were analyzed by means of Chi-square test for nominal variables, Mann–Whitney U, and Kruskal–Wallis test for nonparametric variables. P≤0.05 was taken to indicate a statistical significance.

Results

A total of 320 patients with the diagnosis of focal/self-limited or generalized epilepsy were included in this study. Of these, 51.9% (n=166) were boys. The mean age of epilepsy onset was 7.97±3.38 years (ranging from 1 to 18 years). The mean age at last visit was 21.63±7.16 years (ranging from 1 to 56 years).

The majority of the patients (72.5%, n=232) had focal/self-limited epilepsy. The distribution of epilepsy subtypes is shown in Table 1.

Among the whole group, FS were reported in 14.7% (n=47) of the patients. The rate of FS was similar for boys (15.7%, n=26) and girls (13.6%, n=21) (p=0.362). The onset age of epilepsy did not show significant difference in the presence of FS (p=0.611).

Table 1. Distribution of epilepsy subtypes

		n	%
Focal/Self-limited	Childhood epilepsy with centrotemporal spikes	86	26.9
	Panayiotopoulos syndrome	76	23.8
	Childhood occipital epilepsy (gastaut type)	42	13.1
	Idiopathic photosensitive occipital lobe epilepsy	28	8.8
Generalized	Childhood absence epilepsy	53	16.6
	Juvenile myoclonic epilepsy	35	10.9

Table 2. Frequency of febrile seizures in epilepsy groups

Epilepsy groups	FS (+)		FS (–)		p-value
	n	%	n	%	
Focal/Self-limited	34	14.7	198	85.3	0.552
Generalized	13	14.8	75	85.2	

Table 3. Frequency of febrile seizures in epilepsy subgroups

Epilepsy subgroups	FS (+)		FS (–)		p-value
	n	%	n	%	
Childhood epilepsy with centrotemporal spikes	10	11.6	76	88.4	0.701
Panayiotopoulos syndrome	12	15.8	64	84.2	
Childhood occipital epilepsy (gastaut type)	6	14.3	36	85.7	
Idiopathic photosensitive occipital lobe epilepsy	6	21.4	22	78.6	
Childhood absence epilepsy	6	11.3	47	88.7	
Juvenile myoclonic epilepsy	7	20	28	80	

The ratio of the patients with family history of epilepsy was 25.6% (n=82) while the ratio of the patients with family history of FSs was 15% (n=48).

The rate of having familial history of FS, although not significant, was more frequent in patients with FS (19.1%) than those without FS (14.3%) (p=0.254). The presence of familial history of epilepsy was similar among patients with (23.4%) and without FS (26%) (p=0.430).

The frequency of FSs according to the epilepsy subtypes is given in Tables 2 and 3. Neither the focal/self-limited and generalized epilepsy groups (p=0.552) nor the subtypes of these groups did show significant difference in terms of FS frequency (p=0.701).

Discussion

OFSs are the most common and usually benign seizures of infancy and childhood. Childhood epilepsies, which mostly have a favorable outcome, also present at the similar age-range. Both entities seem to have a genetical background in their pathologies.[12,13] Since FSs are benign with an excellent neurologic outcome and low risk of epilepsy,[14] children with simple FS have approximately the same risk of developing epilepsy by the age of 7 years as the general population.[15,16] The risk factors for epilepsy development include an antecedent neurologic or developmental abnormality, a positive family history of epilepsy, multiple simple FSs, a complex FS (especifically focal FS) and an onset of FSs before 1 year of age.[2,16–19] However, FS cases with preceding positive spikes observed in their EEGs were demonstrated to evolve into epilepsy.[20]

Having a normal neurological or developmental status was an inclusion criteria in the present study. Determining the type and numbers of FS exactly in each patient, which could have helped to understand the effect of FS type association with subsequent epilepsy development, could not be succeeded due to the retrospective design of the study. Nevertheless, the long-term outcome for subsequent epilepsy

was reported to be not influenced by the number or type of FSs.[16,17,21] Offringa et al.[22] reported the ratio of having a family history of FS as 24% in children with FS while the ratio of having a family history of epilepsy was around 4%. The presence of familial history of FS and epilepsy was similar among patients with and without FS in the present study (19.1% and 23.4%; 14.3% and 26%, respectively). Accordingly, the family history of FS and epilepsy did not seem to be a risk factor for epilepsy development.

Camfield et al.[23] suggested that 13–19% of children with AFSs had one or more previous FS. The rate of previous FS (14.7%) was found to be quite similar in our patient group. They also showed that the rate of preceding FSs did not vary with the cause of epilepsy and that FSs most often preceded generalized tonic-clonic AFSs. We did not find any significant differences among the epilepsy groups in terms of FS frequency.

Out of 320 children, 14.7% (n=47) had FS. This ratio was higher than that of the general population which was reported between 2% and 5% in the western world and 3.5% and 9% in Turkey.[24–26] Although ethnic, genetic background or environmental conditions lead to variability among different geographies and knowing that prevalence of FS is higher in developing countries than in developed ones, this ratio still seems high. The reported ratios in the literature are the results of the studies with larger sample size. Hence, our finding may be misleading in that sense. Moreover, arising from the retrospective design of the study (FS history was retrieved from the past medical records), it is a controversial issue whether these seizures are really FS or the seizures triggered by fever.

The frequency of FS did not differ significantly between focal/self-limited and generalized epilepsy groups (ranging between 11.6% and 21.4% and 11.3% and 20%, respectively) supporting the previous literature on the subject. IPOE in focal/self-limited group and JME in generalized group were the epileptic syndromes with the highest ratios of FS occurrence. Considering focal/self-limited epilepsies, reported occurrence of FSs was around 18% in childhood epilepsy with centrotemporal spikes,[27] 17% in Panayiotopoulos syndrome,[28] and 10% in childhood occipital epilepsy of Gastaut type.[29] The cohort studies examining generalized epilepsy patients did not reveal any significant difference between generalized and focal epilepsies. Another study analyzing the long-term outcomes of the patients with CAE reported that 7.7% of patients had a history of FS.[30] There are also some studies reporting the frequency of FS in CAE as high as 20–22% and 13% in JME in the literature.[31] Furthermore, a mutation in a gene encoding a GABA(A) receptor subunit was found in families with epilepsy where the two main phenotypes were CAE and FS[32,33] indicating the genetic relationship between these two syndromes.

Although there was no significant difference in terms of FS frequency within subgroups of epilepsy syndromes, the highest rates, a remarkable finding, were noted in IPOE and JME groups. Photosensitivity is the common feature of these syndromes. The literature has limited number of studies investigating photosensitivity in patients with FS. One study analyzing the photosensitivity in patients with the most common epileptic syndrome revealed that 23% of 117 patients with FS had photosensitivity.[34] This ratio reached up to 42% in a long-term EEG follow-up study.[35] Doose interpreted the photosensitivity as the symptom of genetically independent pathogenetic mechanism which could lead to some additive effects by interacting with other genetic abnormalities as well as exogenous factors, thus denoting that the pathogenesis of febrile convulsions was multifactorial in the strict sense. Based on this finding, a relationship between the photosensitivity and susceptibility to FSs, which may warrant further analysis, may be suggested. However, we should stress that our study could not recognize possible underlying factors in terms of photosensitivity.

It is known that focal seizures may coexist with generalized myoclonic seizures in IPOE. Moreover, Dravet syndrome is characterized with FSs in infancy and myoclonic seizures in the following years. Channelopathy is the common etiological factor among these syndromes. Since the ratio of FS was highest in the epilepsy syndromes with myoclonic seizures in our patient group, we may hypothesize that risk of subsequent development of myoclonic epilepsy is high in FS patients due to this shared etiology of channelopathy.

Conclusion– FSs, although accepted benign, can be a predisposing factor for the development of epilepsy. Gender, family history of epilepsy and FS, onset age of epilepsy, type of epilepsy do not seem as predicting factors for subsequent epilepsy in the patients with FS who were otherwise normal. Additional studies are needed to evaluate the relationship of FSs with photosensitive and myoclonic epilepsies.

Although children with seizures having various etiologies comprise a significant burden in inpatient clinics, the long-term prognosis of epilepsy is favorable in the majority of

children, especially for those with idiopathic etiology. Since the FSs are the most common types of childhood seizures, proper prospective studies on clinicodemographic profile of seizures are required for better understanding the disease burden and to take appropriate measures for its control.

Acknowledgment– This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Informed Consent– Due to the retrospective design of the study, informed consent was not taken.

Peer-review– Externally peer-reviewed.

Authorship Contributions– Concept: F.B.T., M.N., V.D.; Design: F.B.T., M.N., V.D.; Supervision: R.İ., F.Y., V.D.; Data collection &/or processing: F.B.T., M.N.; Analysis and/or interpretation: F.B.T., M.N., R.İ., F.Y., V.D.; Literature search: F.B.T., M.N.; Writing: F.B.T., M.N., R.İ., F.Y., V.D.; Critical review: F.B.T., M.N., R.İ., F.Y., V.D.

Conflict of interest– The authors declare that they have no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

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